

FORM PTO-1390 (Modified)
(REV 11-98)

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER

TRANSMITTAL LETTER TO THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. 371

101195-54

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR

09/869508

INTERNATIONAL APPLICATION NO.

PCT/DE99/04099

INTERNATIONAL FILING DATE

27 December 1999 (27.12.99)

PRIORITY DATE CLAIMED

29 December 1998 (29.12.98)

TITLE OF INVENTION

Gene Transfer Vector for the Diagnosis and Therapy of Malign Tumors

APPLICANT(S) FOR DO/EO/US

Gerhard Wolff; Hans-Dieter Royer; Christiane Woischwill; Martin Janz; and Axel Schumacher

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information.

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1)
4. ☐ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
 - a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☒ has been transmitted by the International Bureau
 - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☐ A copy of the International Search Report (PCT/ISA/210).
8. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
 - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☐ have been transmitted by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired
 - d. ☐ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
10. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
11. ☐ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 13 to 20 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☒ Certificate of Mailing by Express Mail
20. ☐ Other items or information:

ATTORNEY'S DOCKET NUMBER

101195-54

21. The following fees are submitted:.

CALCULATIONS PTO USE ONLY

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

- | | | |
|-------------------------------------|---|-------------------|
| <input type="checkbox"/> | Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO | \$1,000.00 |
| <input checked="" type="checkbox"/> | International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO | \$860.00 |
| <input type="checkbox"/> | International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO | \$710.00 |
| <input type="checkbox"/> | International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) | \$690.00 |
| <input type="checkbox"/> | International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) | \$100.00 |

ENTER APPROPRIATE BASIC FEE AMOUNT =

\$860.00

Surcharge of **\$130.00** for furnishing the oath or declaration later than months from the earliest claimed priority date (37 CFR 1.492 (e)). ☐ 20 ☒ 30

\$130.00

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	- 20 =	0	x \$18.00	\$0.00
Independent claims	- 3 =	0	x \$80.00	\$0.00
Multiple Dependent Claims (check if applicable).			<input type="checkbox"/>	\$0.00

Multiple Dependent Claims (check if applicable).

TOTAL OF ABOVE CALCULATIONS

\$990.00

Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) (check if applicable)

\$495.00

SUBTOTAL

\$495.00

Processing fee of **\$130.00** for furnishing the English translation later than ☐ 20 ☒ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)).

\$130.00

TOTAL NATIONAL FEE**\$625.00**

Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable)**.

\$0.00

TOTAL FEES ENCLOSED

\$625.00

**Amount to be:
refunded**

\$

charged

\$

- ☐ A check in the amount of _____ to cover the above fees is enclosed.
- ☒ Please charge my Deposit Account No. **14-1263** in the amount of **\$625.00** to cover the above fees.
A duplicate copy of this sheet is enclosed.
- ☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. **14-1263** A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

the correspondence address associated with customer no. 27387



27387

PATENT TRADEMARK OFFICE

SIGNATURE

Bruce S. Londa

NAME _____

33.531

REGISTRATION NUMBER

June 28, 2001

DATE _____

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
Atty's Docket No. 101195-54

APPLICANT : Gerhard Wolff et al.
FILED : Concurrently Herewith
FOR : Gene Transfer Vector for the Diagnosis and
Therapy of Malign Tumors

PRELIMINARY AMENDMENT

Hon. Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Prior to examination, please amend the application as
follows:

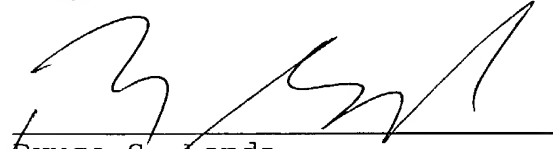
IN THE CLAIMS

Please make claims 4 to 15 solely dependent on claim 1.

REMARKS

The above amendments were made to eliminate multiple
dependent claims.

Respectfully Submitted,



Bruce S. Londa
Attorney for Applicant
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~~09/869,508~~
Rec'd PET/PTC 26 FEB 2002

PATENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
Atty's Docket No. 101195-54

EXAMINER :
GROUP ART UNIT :
APPLICANT : Gerhard Wolff, et al.
APPLN. NUMBER : 09/869,508
FILED : June 28, 2001
FOR : Gene Transfer Vector for the Diagnosis and
Therapy of Malign Tumors

PRELIMINARY AMENDMENT

Hon. Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Prior to examination, please amend the application as
follows:

IN THE SPECIFICATION

Page 1, after line 2, please insert --Background of the
Invention--;

Page 4, after line 4, please insert --Summary of the
Invention--;

Page 5, after line 19, please insert

--Brief Description of the Drawings--

Fig. 1 - chart illustrating the expression cassette;

Fig. 2 - chart illustrating a kind of "box-of-bricks" system in which the therapeutic genes can be replaced with a low amount of effort;

Fig. 3 - chart illustrating the generation of a recombinant adenoviral plasmide containing the expressing cassette by homologous recombination in the BJ cells;

Fig. 4a- graft showing the constitutive promoter leading to a continuous increase of the serum content of hAAT; and

Fig. 4b- graft showing the Ad vector with the YB-a promoter leading to a temporarily very high expression with a maximum serum content of hAAT on the third day.

Description of the Preferred Embodiment--.

IN THE CLAIMS

Please amend the claims as follows. A clean copy is also enclosed.

1. Gene transfer vector, comprising
 - the YB-1 promoter, its mutants or deletion variants,
 - a transgene or the cDNA of a transgene

- two multi-cloning sites (MCS) suited to cutting out the transgene for restriction enzymes surrounding the transgene.

2. Gene transfer vector according to Claim 1, wherein the transgene is a therapeutic gene.

3. Gene transfer vector according to Claim 1, wherein the transgene is a reporter gene.

4. (amended) Gene transfer vector according to Claim 1, wherein the therapeutic gene is a cell-cycle regulating or a proapoptotic gene.

5. (amended) Gene transfer vector according to Claim 1, wherein p16, p21, p53 or Bax is used as a therapeutic gene.

6. (amended) Gene transfer vector according to Claim 1, wherein a regulating element is additionally inserted into the vector.

7. (amended) Gene transfer vector according to Claim 1, wherein the multi-cloning sites (MCS) contain at least 3 enzyme restriction sites interfaces for restriction enzymes.

8. (amended) Gene transfer vector according to Claim 1, wherein the multi-cloning sites (MCS) contain enzyme restriction sites for restriction enzymes 5-10.

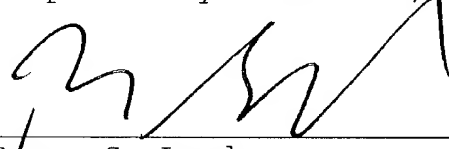
9. (amended) Gene transfer vector according to Claim 1, wherein the multi-cloning sites (MCS) for restriction enzymes contain no enzyme restriction sites occurring within the sequences of the YB-1 promoter.

10. (amended) Gene transfer vector according to Claim 1, wherein the multi-cloning sites (MCS) contain sticky enzyme restriction sites and blunt enzyme restriction sites for restriction enzymes.

REMARKS

The above amendments were made to place the application into proper United States Patent Format.

Respectfully Submitted,



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Amended Claims - Marked-Up Copy

1. Gene transfer vector, comprising
 - the YB-1 promoter, its mutants or deletion variants,
 - a transgene or the cDNA of a transgene
 - two multi-cloning sites (MCS) suited to cutting out the transgene for restriction enzymes surrounding the transgene.
2. Gene transfer vector according to Claim 1, wherein the transgene is a therapeutic gene.
3. Gene transfer vector according to Claim 1, wherein the transgene is a reporter gene.
4. (amended) Gene transfer vector according to ~~Claims 1 and 2~~ Claim 1, wherein the therapeutic gene is a cell-cycle regulating or a proapoptotic gene.
5. (amended) Gene transfer vector according to ~~Claims 1, 2 and 4~~ Claim 1, wherein p16, p21, p53 or Bax is used as a therapeutic gene.
6. (amended) Gene transfer vector according to ~~Claims 1-5~~ Claim 1, wherein a regulating element is additionally inserted into the vector.

Amended Claims - Marked-Up Copy

7. (amended) Gene transfer vector according to ~~Claim 1-6~~ Claim 1, wherein the multi-cloning sites (MCS) contain at least 3 enzyme restriction sites interfaces for restriction enzymes.

8. (amended) Gene transfer vector according to ~~Claims 1-7~~ Claim 1, wherein the multi-cloning sites (MCS) contain enzyme restriction sites for restriction enzymes 5-10.

9. (amended) Gene transfer vector according to ~~Claims 1-8~~ Claim 1, wherein the multi-cloning sites (MCS) for restriction enzymes contain no enzyme restriction sites occurring within the sequences of the YB-1 promoter.

10. (amended) Gene transfer vector according to ~~Claims 1-9~~ Claim 1, wherein the multi-cloning sites (MCS) contain sticky enzyme restriction sites and blunt enzyme restriction sites for restriction enzymes.

~~11. Use of the vector according to Claims 1-10 for the treatment of tumours.~~

~~12. Use of the vector according to Claims 1-10 for the treatment of chemo-resistant tumours.~~

Amended Claims - Marked-Up Copy

~~13. Use of the vector according to Claims 1-10 for the treatment of chemo-sensitive tumours.~~

~~14. Use of the vector according to Claims 1-10 for the treatment of breast cancer.~~

~~15. Use of the vector according to Claims 1-10 for the micro-localisation of tumours.~~

Gene transfer vector for the diagnosis and the therapy of malign
tumours

The invention relates to a new gene transfer vector and its use,
in particular for the treatment of chemo-resistant tumour cells.

It is known that about 50% of all tumours cannot be treated as
they are "multi-drug resistant". For example, breast cancer cells
can be either primarily resistant against chemotherapy or can
develop this resistance in a later phase after initially
successful therapy (secondary therapy resistance).

Such a resistant phenotype can result from the over-expression of
a transporter protein. This so-called *P-Glycoprotein* forms a kind
of pump for example for the above mentioned chemotherapy as a
trans-membrane protein, by which these therapeutics are
transported back into the extra-cellular area. The *P-Glycoprotein*
is coded by the *MDR-1* ("Multi-drug resistance") gene, which is
regulated on a transcriptional level by the *YB-1* binding protein,
the latter binding on the "Y box" within the DNA sequence of the
MDR-1 gene (Van Veen and Konings et al, 1997, Sem Cancer Biol,
8, 183-191).

The *YB-1* promoter controls the expression of the *YB-1* protein,
which is a member of the family of the "Y box" binding proteins.
These Y box factors belong to a highly conserved class of

proteins which play a role in the regulation of *transcription* and *translation*. The proteins bind to a sequence within the DNA of a target gene (the so-called Y box sequence), by which the expression of this gene results (Bargou et al, 1997, Nat Med, 3, 447-450).

YB-1 is strongly expressed in the course of cell proliferation and can be induced by genotoxic substances, e.g. chemotherapeutics, UV light and ionising radiation (Koike et al, 1997, Febs Lett, 417, 390-394). In addition, it has been established that the expression of YB-1 is considerably increased in proliferating cells such as embryonal and regenerating tissues, whereas this condition is reversed in tissue differentiation (Grant and Deeley, 1993, Mol Cell Biol, 12, 4186-4196, Spitkovsky et al, 1992, Nucleic Acids Res, 20, 797-803).

Our own studies have shown that the over-expression of the MDR-1 gene in breast cancer cells and the intrinsic multi-drug resistance connected therewith are connected with the activity and localisation of the YB-1 protein (Bargou et al, 1997, Nat Med, 3, 447-450).

In cases of chemo-resistance, it is therefore necessary to find an alternative to the use of chemo-therapeutics.

It is known that gene therapy is used for the treatment of acquired and inherited diseases, with it being a question of the transfer of a therapeutic gene, for example a tumour suppressor gene. Various vector systems are available in this context, in order to achieve the highest possible share of cells of the target tissue in the gene transfer. In this, viral vectors have proven to be most suited up to now. Adenoviral vectors are being used increasingly more often as they can infect a plurality of tumour tissues with great effectivity. Each of these vectors contains a specific expression cassette (EC), which enters the target cell through the adenoviral infection. This expression cassette comprises a promoter and a therapeutic gene, with the promoter ensuring the expression of the gene in the target cells. Promoters frequently used are, for example, SV40, RSV and CMV (Sandig et al, 1997, Nat med, 3, 313-319).

The fact that adenoviruses can infect a number of types of tissue is, on the one hand, a benefit of this gene transfer system. Customary adenoviral strategies, on the other hand, are insufficient in certain diseases/therapies. It is therefore necessary to develop therapies in which the gene expression is only restricted to certain cells. This can be achieved by *tissue-specific promoters*. The use, for example, of tumour-specific promoters creates the possibility of only expressing the therapeutic gene in the tumour tissue and not in the adjoining,

likewise infected standard tissue (Robbins et al, 1998, Trends Biotechnol, 16, 35-40). In this way, the target precision of the gene transfer is increased, by which it becomes possible also to use therapeutic genes which are damaging for normal cells.

The invention was thus based on the task of developing a vector with an expression cassette containing a tumour-specific promoter which only expresses a relevant gene in chemo-resistant tumour cells. This gene therapy vector is thus to be used in tumour cells which are already chemo-resistant and thus no longer react to a conventional chemotherapy.

On the one hand, the cassette is to be constructed in such a way that it can be cloned into various gene transfer vectors, for example adenoviral vectors. On the other hand, it is simultaneously to be possible to clone the varied therapeutic genes into this cassette "downstream" from the promoter without great technical efforts.

The task is solved according to the patent claims by a vector possessing the following components: the YB-1 promoter, a transgene and two "multiple cloning sites" (MCS). In this, the tumour-specific YB-1 promoter is to bring a transgene to expression in chemo-resistant tumour cells by adenoviral gene transfer. This transgene can be a therapeutically relevant gene

[illegible]

The new gene transfer vector can be used for the treatment of tumours. Preferably, it is suitable for the treatment of chemoresistant tumours. A further possibility of application is in diagnosis (micro-localisation of tumours).

To start with, the corresponding therapeutic gene is cloned behind the YB-1 promoter (nucleotide 259-294 of the MCS of the

pCR2.1 vector of Invitrogen and nucleotide 453-2150 of the YB-1 promoter sequence, gene bank Acc.# X96666). These two elements represent the expression cassette (see Fig. 1). In this, the YB-1 promoter is cloned into an MSC of a vector adapted specifically for this purpose in such a way that various therapeutic genes can be put under the control of the promoter without the MCS having to be adapted again. This is a MCS containing a group of specifically selected enzyme restriction sites. These restriction sites are to permit a quick and uncomplicated exchange of the therapeutic genes into the expression cassette "downstream" of the promoter. Additional changes to the remaining vector and to the YB-1 promoter already existing are avoided in this way. Thus, there results a kind of "box-of-bricks" system in which the therapeutic genes can be replaced with a low amount of effort (see Fig. 2).

The expression cassette containing the YB-1 promoter and the therapeutic gene is then cloned into a so-called transfer plasmide (TP). This plasmide contains a part of the adenoviral genome. For this step, the enzyme restriction sites of the MCS surrounding the EC and also existent in the transfer plasmide are used. The TP is then transformed into bacteria (BJ cells) with the "helper plasmide" (HP). The helper plasmide possesses the entire adenoviral genome with the exception of the E1 and E3 region, with the E1 deletion making the virus replication-

deficient. As the adenoviral genome sections surrounding the EC in the TP have a homology with certain sections of the genome of the HP, a recombinant adenoviral plasmide containing the expression cassette (see Fig. 3) is generated by homologous recombination in the BJ cells. By gene transfer techniques such as calcium phosphate precipitation or liposomes, this recombinant adenoviral plasmide is then inserted into a production cell line (293; human, embryonal renal cell line), in order to lead to production of replication-deficient viruses. The latter contain the therapeutic gene under the control of the tumour-specific YB-1 promoter. After this, tumours of chemo-resistant cell lines are established in various mouse strains (SCID and nude mice) (e.g. of epithelial origin), which are then infected with the recombinant virus. The measurement of the transgene expression by e.g. ELISA and immuno-histochemical techniques and its effect on the tumour are then analysed with regard to a possible therapeutic approach.

EXAMPLE OF EMBODIMENT 2

The invention was checked in vivo for the proliferation-specific activity of the YB-1 promoter in an animal model. It is known that adenoviral vectors drive hepatocytes into proliferation on the third day after vector application. For this reason, two adenoviral vectors were compared in SCID mice with human alpha 1-

antitrypsin (hAAT), which were only distinguished by the promoter (AdYB-1.hAAT or AdRSV.hAAT) in a liver gene transfer model.

The constitutive promoter led to a continuous increase of the serum content of hAAT (Fig. 4A). In contract, the Ad vector with the YB-1 promoter led to a temporarily very high expression with a maximum serum content of hAAT on the third day (Fig. 4B).

1.0×10^9 pfu AdRSV.hAAT (A) or AdYB-1.hAAT (B) was injected intravenously into SCID mice (n=3 for A and B). The serum content of human alpha 1-antitrypsin (hAAT) was determined by means of ELISA.

In this way, the proliferation-specific activity of the YB-1 promoter was proven.

$\frac{d}{dt} \left(\frac{\partial L}{\partial \dot{x}} \right) = \frac{\partial L}{\partial x}$

$\frac{d}{dt} \left(\frac{\partial L}{\partial \dot{x}} \right) = \frac{\partial L}{\partial x}$

- [illegible]

[illegible]

7. Gene transfer vector according to Claim 1-6, wherein the multi-cloning sites (MCS) contain at least 3 enzyme restriction sites interfaces for restriction enzymes.
8. Gene transfer vector according to Claims 1-7, wherein the multi-cloning sites (MCS) contain enzyme restriction sites for restriction enzymes 5-10.
9. Gene transfer vector according to Claims 1-8, wherein the multi-cloning sites (MCS) for restriction enzymes contain no enzyme restriction sites occurring within the sequences of the YB-1 promoter.
10. Gene transfer vector according to Claims 1-9, wherein the multi-cloning sites (MCS) contain sticky enzyme restriction sites and blunt enzyme restriction sites for restriction enzymes.
11. Use of the vector according to Claims 1-10 for the treatment of tumours.
12. Use of the vector according to Claims 1-10 for the treatment of chemo-resistant tumours.
13. Use of the vector according to Claims 1-10 for the treatment of chemo-sensitive tumours.

ABSTRACT

The invention relates to a gene transfer vector for diagnosis and therapy of malign tumours, coding for an arbitrary transgene under the control of the tumour-specific YB-1 promoter. It comprises the YB-1 promoter, a transgene and two "multiple cloning sites" surrounding the transgene suited for restriction enzymes for cutting out the transgene. An arbitrary gene can be cloned into the construction, in order to be expressed tissue-specifically into chemo-resistant tumour cells.

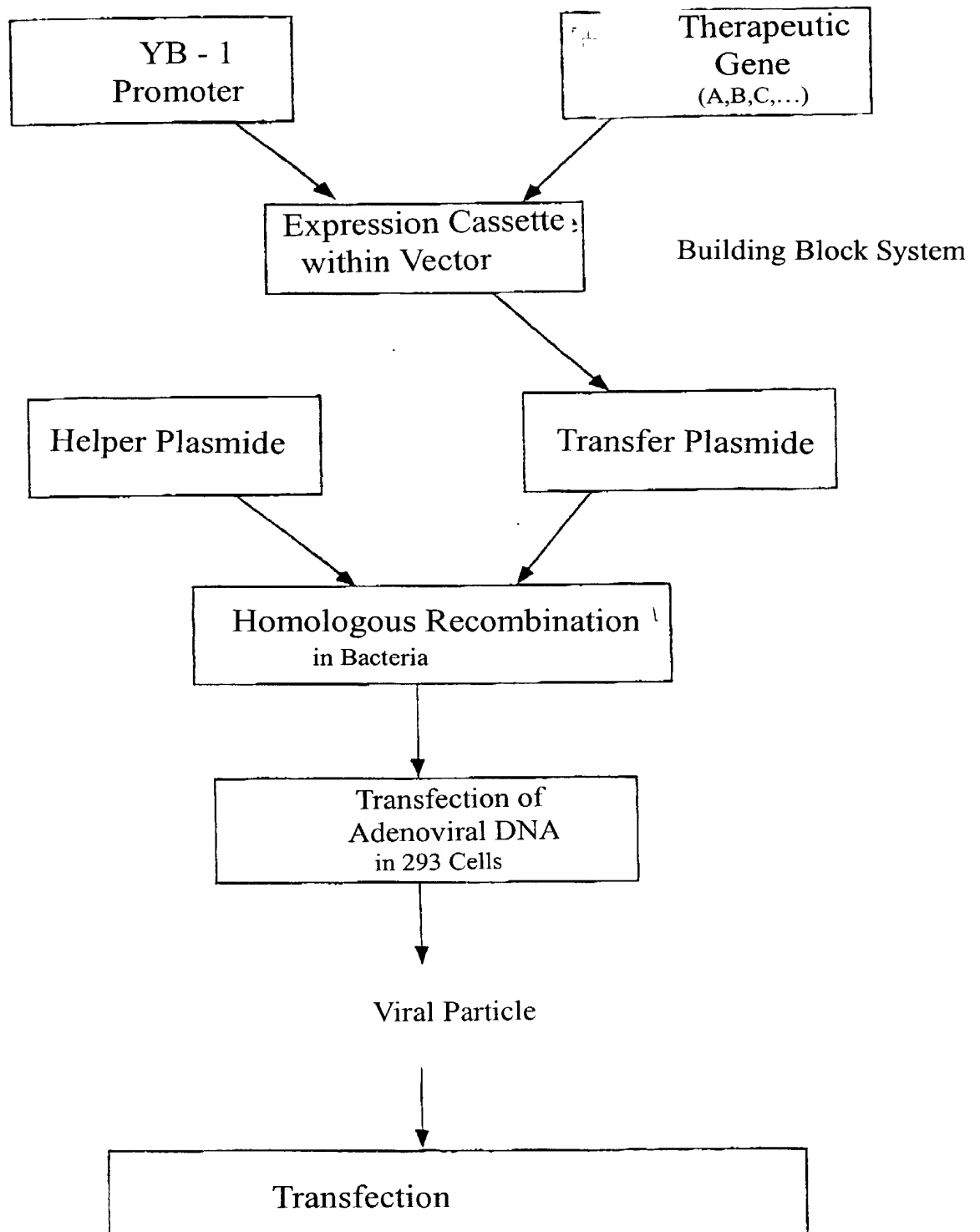


Fig. 1

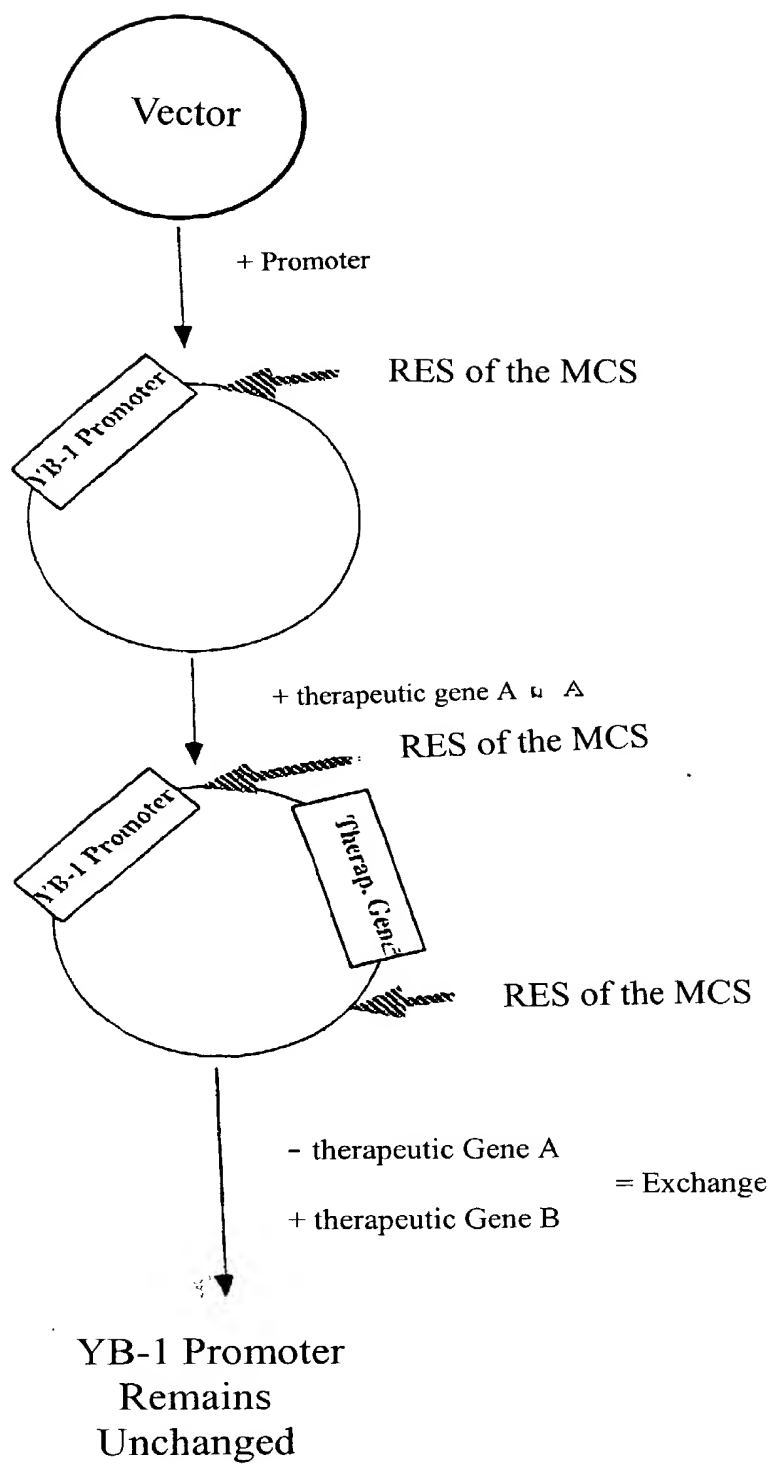


Fig. 2

Homologous Recombination in Bacterium

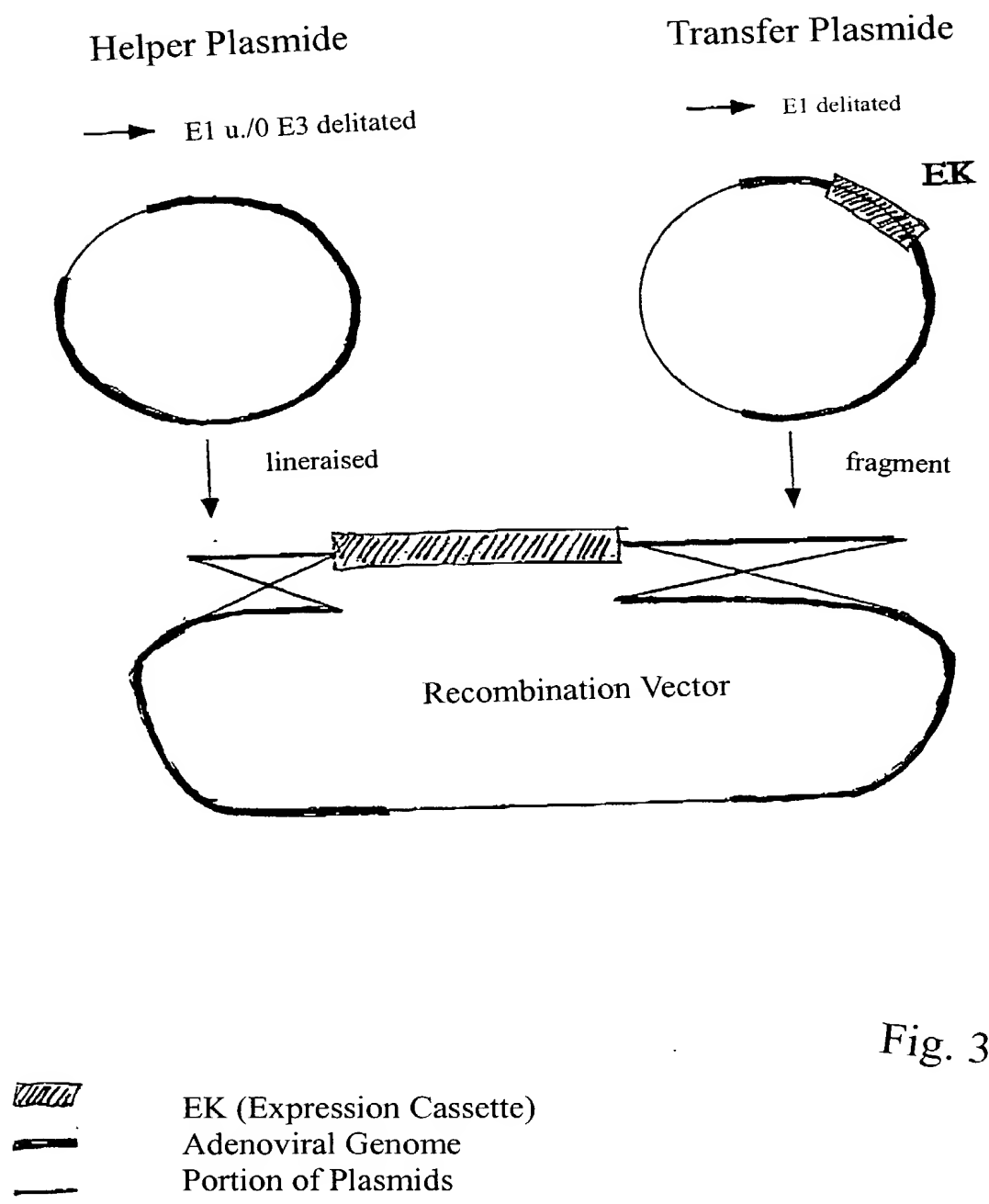


Fig. 3

Fig. 4 A

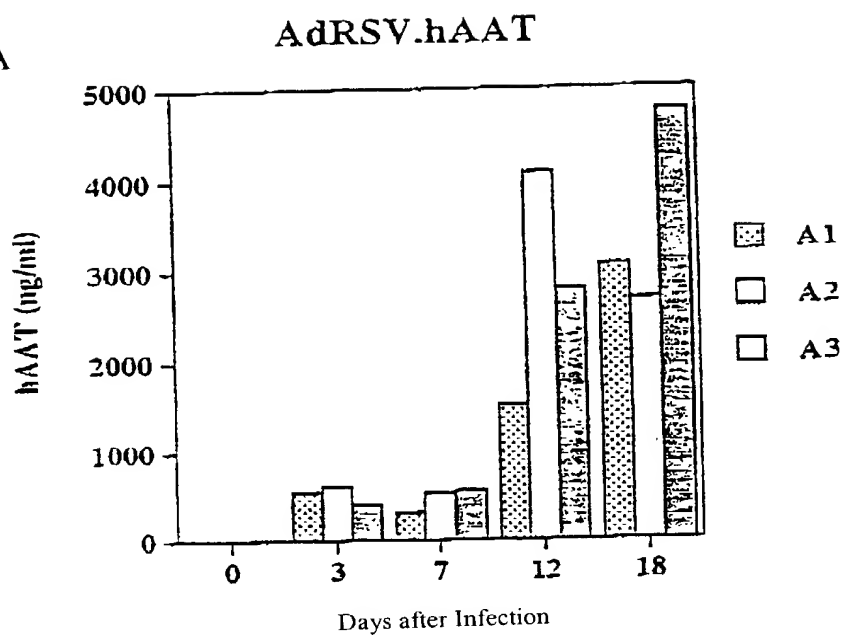
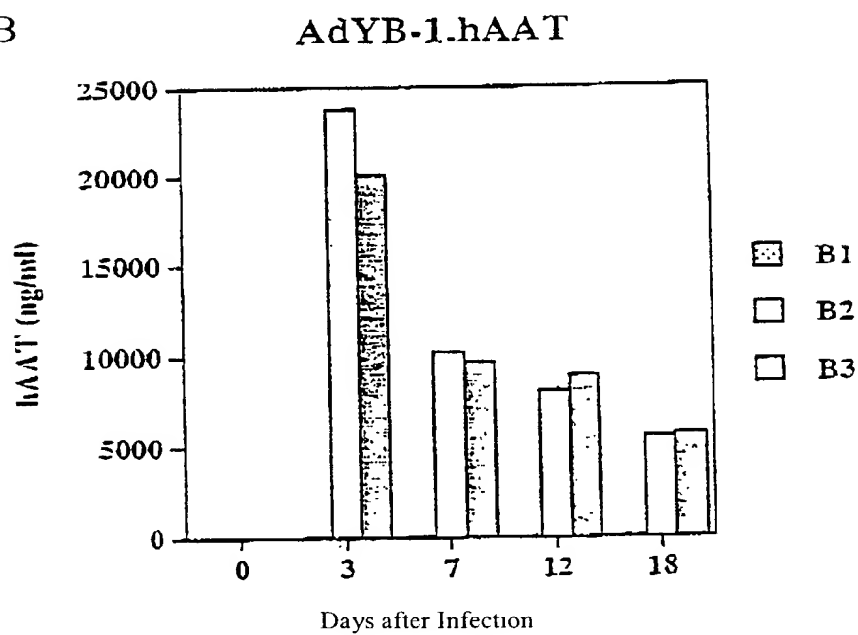


Fig. 4 B



Norris, McLaughlin & Marcus, P.A.

220 East 42nd Street, 30th Floor
New York, NY 10017

If each inventor understands English, the Declaration and Power of Attorney below is suitable for use when filing a regular patent application and also when entering the national stage, in the case of an International application designating the USA under the PCT.

COMBINED DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION			Attorney Docket No. 101195-54																						
<p>As a below named inventor, I hereby declare that: My residence, post office address and citizenship are as stated below next to my name. I believe I am the original, first and sole inventor (if only one name is listed below at 201) or an original, first and joint inventor (if plural names are listed below at 201-210) of the subject matter which is claimed and for which a patent is sought on the invention entitled</p> <p>Gene Transfer Vector for the Diagnosis and Therapy of Malign Tumors</p> <p>the specification of which (check one)</p> <p><input type="checkbox"/> is attached hereto</p> <p><input checked="" type="checkbox"/> was filed on <u>27 December 1999</u></p> <p>under Serial Number <u>PCT/DE99/04099</u> and was amended on <u>20/03/2001</u> (if applicable).</p> <p>I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.</p> <p>I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, Section 1.56.</p> <p>I list below any prior foreign application(s) for patent or inventor's certificate in respect of which foreign priority benefits are claimed under 35 USC 119; and any prior foreign application(s) for patent or inventor's certificate in respect of which such foreign priority rights are not claimed and which has a filing date before that of any application in respect of which such foreign priority benefits are claimed:</p> <table border="1"> <thead> <tr> <th>Application Number</th> <th>Country</th> <th>Filing Date (day, month, year)</th> <th>Priority Claimed under 35 USC 119</th> </tr> </thead> <tbody> <tr> <td>198 60 602.8</td> <td>Germany</td> <td>29 December 1998</td> <td>YES: <input checked="" type="checkbox"/> NO: <input type="checkbox"/></td> </tr> <tr> <td></td> <td></td> <td></td> <td>YES: <input type="checkbox"/> NO: <input type="checkbox"/></td> </tr> <tr> <td></td> <td></td> <td></td> <td>YES: <input type="checkbox"/> NO: <input type="checkbox"/></td> </tr> </tbody> </table> <p>I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below.</p> <table border="1"> <thead> <tr> <th>Application No.</th> <th>Filing Date</th> </tr> </thead> <tbody> <tr> <td></td> <td></td> </tr> <tr> <td></td> <td></td> </tr> </tbody> </table>				Application Number	Country	Filing Date (day, month, year)	Priority Claimed under 35 USC 119	198 60 602.8	Germany	29 December 1998	YES: <input checked="" type="checkbox"/> NO: <input type="checkbox"/>				YES: <input type="checkbox"/> NO: <input type="checkbox"/>				YES: <input type="checkbox"/> NO: <input type="checkbox"/>	Application No.	Filing Date				
Application Number	Country	Filing Date (day, month, year)	Priority Claimed under 35 USC 119																						
198 60 602.8	Germany	29 December 1998	YES: <input checked="" type="checkbox"/> NO: <input type="checkbox"/>																						
			YES: <input type="checkbox"/> NO: <input type="checkbox"/>																						
			YES: <input type="checkbox"/> NO: <input type="checkbox"/>																						
Application No.	Filing Date																								

Combined Declaration and Power of Attorney

101195-54

Page 2

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Bruce S. Londa (33,531) Lorimer P. Brooks (15,155) William R. Robinson (27,224)
Kurt G. Brisco (33,141) William C. Gerstenzang (27,552) Robert A. Hyde (46,354)
Davy E. Zoneraich (37,267) Mark A. Montana (44,948)

201	Family Name	First Given Name	Second Given Name
	DÖRKEN	Bernd	
	City of Residence	State or Foreign Country	Country of Citizenship
	Berlin	Germany	Germany
	Post Office Address	City	State & ZIP/Country
	Lyckallee 47	D-14055 Berlin	Germany
	Family Name	First Given Name	Second Given Name
	WOLFF	Gerhard	
202	City of Residence	State or Foreign Country	Country of Citizenship
	Berlin	Germany	Germany
	Post Office Address	City	State & ZIP/Country
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	Post Office Address	City	State & ZIP/Country
209	Family Name	First Given Name	Second Given Name
	City of Residence	State or Foreign Country	Country of Citizenship
	Post Office Address	City	State & ZIP/Country

1. 2. 3. 4. 5. 6. 7. 8. 9. 10. 11. 12. 13. 14. 15. 16. 17. 18. 19. 20. 21. 22. 23. 24. 25. 26. 27. 28. 29. 30. 31. 32. 33. 34. 35. 36. 37. 38. 39. 40. 41. 42. 43. 44. 45. 46. 47. 48. 49. 50. 51. 52. 53. 54. 55. 56. 57. 58. 59. 60. 61. 62. 63. 64. 65. 66. 67. 68. 69. 70. 71. 72. 73. 74. 75. 76. 77. 78. 79. 80. 81. 82. 83. 84. 85. 86. 87. 88. 89. 90. 91. 92. 93. 94. 95. 96. 97. 98. 99. 100. 101. 102. 103. 104. 105. 106. 107. 108. 109. 110. 111. 112. 113. 114. 115. 116. 117. 118. 119. 120. 121. 122. 123. 124. 125. 126. 127. 128. 129. 130. 131. 132. 133. 134. 135. 136. 137. 138. 139. 140. 141. 142. 143. 144. 145. 146. 147. 148. 149. 150. 151. 152. 153. 154. 155. 156. 157. 158. 159. 160. 161. 162. 163. 164. 165. 166. 167. 168. 169. 170. 171. 172. 173. 174. 175. 176. 177. 178. 179. 180. 181. 182. 183. 184. 185. 186. 187. 188. 189. 190. 191. 192. 193. 194. 195. 196. 197. 198. 199. 200. 201. 202. 203. 204. 205. 206. 207. 208. 209. 210. 211. 212. 213. 214. 215. 216. 217. 218. 219. 220. 221. 222. 223. 224. 225. 226. 227. 228. 229. 230. 231. 232. 233. 234. 235. 236. 237. 238. 239. 240. 241. 242. 243. 244. 245. 246. 247. 248. 249. 250. 251. 252. 253. 254. 255. 256. 257. 258. 259. 260. 261. 262. 263. 264. 265. 266. 267. 268. 269. 270. 271. 272. 273. 274. 275. 276. 277. 278. 279. 280. 281. 282. 283. 284. 285. 286. 287. 288. 289. 290. 291. 292. 293. 294. 295. 296. 297. 298. 299. 300. 301. 302. 303. 304. 305. 306. 307. 308. 309. 310. 311. 312. 313. 314. 315. 316. 317. 318. 319. 320. 321. 322. 323. 324. 325. 326. 327. 328. 329. 330. 331. 332. 333. 334. 335. 336. 337. 338. 339. 340. 341. 342. 343. 344. 345. 346. 347. 348. 349. 350. 351. 352. 353. 354. 355. 356. 357. 358. 359. 360. 361. 362. 363. 364. 365. 366. 367. 368. 369. 370. 371. 372. 373. 374. 375. 376. 377. 378. 379. 380. 381. 382. 383. 384. 385. 386. 387. 388. 389. 390. 391. 392. 393. 394. 395. 396. 397. 398. 399. 400. 401. 402. 403. 404. 405. 406. 407. 408. 409. 410. 411. 412. 413. 414. 415. 416. 417. 418. 419. 420. 421. 422. 423. 424. 425. 426. 427. 428. 429. 430. 431. 432. 433. 434. 435. 436. 437. 438. 439. 440. 441. 442. 443. 444. 445. 446. 447. 448. 449. 450. 451. 452. 453. 454. 455. 456. 457. 458. 459. 460. 461. 462. 463. 464. 465. 466. 467. 468. 469. 470. 471. 472. 473. 474. 475. 476. 477. 478. 479. 480. 481. 482. 483. 484. 485. 486. 487. 488. 489. 490. 491. 492. 493. 494. 495. 496. 497. 498. 499. 500. 501. 502. 503. 504. 505. 506. 507. 508. 509. 510. 511. 512. 513. 514. 515. 516. 517. 518. 519. 520. 521. 522. 523. 524. 525. 526. 527. 528. 529. 530. 531. 532. 533. 534. 535. 536. 537. 538. 539. 540. 541. 542. 543. 544. 545. 546. 547. 548. 549. 550. 551. 552. 553. 554. 555. 556. 557. 558. 559. 560. 561. 562. 563. 564. 565. 566. 567. 568. 569. 570. 571. 572. 573. 574. 575. 576. 577. 578. 579. 580. 581. 582. 583. 584. 585. 586. 587. 588. 589. 590. 591. 592. 593. 594. 595. 596. 597. 598. 599. 600. 601. 602. 603. 604. 605. 606. 607. 608. 609. 610. 611. 612. 613. 614. 615. 616. 617. 618. 619. 620. 621. 622. 623. 624. 625. 626. 627. 628. 629. 630. 631. 632. 633. 634. 635. 636. 637. 638. 639. 640. 641. 642. 643. 644. 645. 646. 647. 648. 649. 650. 651. 652. 653. 654. 655. 656. 657. 658. 659. 660. 661. 662. 663. 664. 665. 666. 667. 668. 669. 670. 671. 672. 673. 674. 675. 676. 677. 678. 679. 680. 681. 682. 683. 684. 685. 686. 687. 688. 689. 690. 691. 692. 693. 694. 695. 696. 697. 698. 699. 700. 701. 702. 703. 704. 705. 706. 707. 708. 709. 710. 711. 712. 713. 714. 715. 716. 717. 718. 719. 720. 721. 722. 723. 724. 725. 726. 727. 728. 729. 730. 731. 732. 733. 734. 735. 736. 737. 738. 739. 740. 741. 742. 743. 744. 745. 746. 747. 748. 749. 750. 751. 752. 753. 754. 755. 756. 757. 758. 759. 760. 761. 762. 763. 764. 765. 766. 767. 768. 769. 770. 771. 772. 773. 774. 775. 776. 777. 778. 779. 780. 781. 782. 783. 784. 785. 786. 787. 788. 789. 790. 791. 792. 793. 794. 795. 796. 797. 798. 799. 800. 801. 802. 803. 804. 805. 806. 807. 808. 809. 810. 811. 812. 813. 814. 815. 816. 817. 818. 819. 820. 821. 822. 823. 824. 825. 826. 827. 828. 829. 830. 831. 832. 833. 834. 835. 836. 837. 838. 839. 840.

Page 4

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signature of Inventor 201

Date _____

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Signature of Inventor 202

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| Date |
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Signature of Inventor 203

Date _____

19/08/01

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24/8/09

Signature of Inventor 205

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Signature of Inventor 210

Date _____

If each inventor understands English, the Declaration and Power of Attorney below is suitable for use when filing a regular patent application and also when entering the national stage, in the case of an International application designating the USA under the PCT.

20. März 02

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I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

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|------------|---------------------|--------------------------|------------------------|
| 210 | Family Name | First Given Name | Second Given Name |
| | City of Residence | State or Foreign Country | Country of Citizenship |
| | Post Office Address | City | State & ZIP/Country |

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

| | |
|---|------------------------|
| Signature of Inventor 201 | Date |
| Signature of Inventor 202 <i>X</i> <i>[Signature]</i> | Date <i>X</i> 05/13/02 |
| Signature of Inventor 203 | Date |
| Signature of Inventor 204 | Date |
| Signature of Inventor 205 | Date |
| Signature of Inventor 206 | Date |
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| Signature of Inventor 210 | Date |

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Jul-02-01 12:37pm From-Norris McLaughlin & Marcus

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ADDED PAGE TO COMBINED DECLARATION
AND POWER OF ATTORNEY FOR SIGNATURE BY JOINT INVENTORS
ON BEHALF OF NONSIGNING INVENTOR WHO REFUSES
TO SIGN OR CANNOT BE REACHED (37.CFR1.47(a))

I. I am an above named joint inventor and have signed this declaration on my own behalf and also sign this declaration under 37 CFR 1.47(a) on behalf of the nonsigning joint inventor, particulars for whom are:

Full Name of second nonsigning inventor, Gerhard Wolff,

who refuses to sign and cannot be found or reached.

Country of citizenship of nonsigning inventor - Germany

Last known address of nonsigning inventor - Karl-Liebkecht-Strasse 23,
16548 Glienicke (Nordbahn), Germany

II. Accompanying this declaration is:

1. A Statement of Facts in Support of Filing on Behalf of Nonsigning Inventor
2. The Petition Fee of \$130.00 (37 CFR1.17(i))

x 
Bernd Dörken

Hans-Dieter Royer

Christiane Woischwill

Martin Janz

Axel Schumacher

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ON BEHALF OF NONSIGNING INVENTOR WHO REFUSES
TO SIGN OR CANNOT BE REACHED (37.CFR1.47(a))

I. I am an above named joint inventor and have signed this declaration on my own behalf and also sign this declaration under 37 CFR 1.47(a) on behalf of the nonsigning joint inventor, particulars for whom are:

Full Name of second nonsigning inventor, Gerhard Wolff,

who refuses to sign and cannot be found or reached.

Country of citizenship of nonsigning inventor - Germany

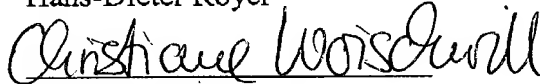
Last known address of nonsigning inventor - Karl-Liebkecht-Strasse 23,
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II. Accompanying this declaration is:

1. A Statement of Facts in Support of Filing on Behalf of Nonsigning Inventor
2. The Petition Fee of \$130.00 (37 CFR1.17(i))

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Country of citizenship of nonsigning inventor - Germany

Last known address of nonsigning inventor - Karl-Liebkecht-Strasse 23,
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Hans-Dieter Royer

Christiane Woischwill

x Martin Janz

Martin Janz

Axel Schumacher